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Misdiagnosis During the COVID-19 Pandemic: A Case of Lymphoma Initially Diagnosed as Coronavirus Infection

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Abstract

Introduction: During the coronavirus disease 2019 (COVID-19) pandemic, physicians delivered a leading part and carried a high work volume, leading to burnout, which subsequently compromised patient safety, decreased the quality of care, and increased misdiagnosis. In the course of the COVID-19 pandemic, physicians should have been vigilant and informed about the potential conditions resulting in medical errors. Particularly, epidemics of infectious illnesses can cause serious challenges in lymphoma diagnosis.

Case Presentation: This case report presents a patient with lymphoma presenting with cough, fever, shortness of breath, and a history of contact with her family members who tested positive for COVID-19, which caused delayed diagnosis and treatment, disease progression, and finally, the death of the patient. In the course of the COVID-19 pandemic, the center of attention was detracted from other possible diagnoses, thereby missing lymphoma as a potentially treatable disease.

Conclusions: Although physicians are required to be watchful for COVID-19 amid the pandemic, it is also necessary not to neglect other diseases. A delay in the initiation of cancer therapy, even for one month, has been reported to increase the risk of mortality by approximately 10%.

Keywords: Misdiagnosis, COVID-19, Lymphoma, Coronavirus

1. Introduction

The novel coronavirus disease 2019 (COVID-19), recognized as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is regarded as a critical public health issue. Severe pneumonia and acute respiratory distress syndrome are distinct features of COVID-19, causing a remarkably high rate of mortality (1).

Amid the COVID-19 pandemic, physicians, due to their leading role in health provision, were exposed to high work burdens. During the pandemic, physical exhaustion and mental distress due to the fear of contracting the infection led most clinicians to spend the least possible time with patients (2). Furthermore, several factors, such as the prolonged wearing of personal protective clothing with extreme heat, insufficient hydration, poor nutrition, sleep deprivation, and extra work shifts, all at once made tiredness and burnout inevitable consequences. On the other hand, physician burnout compromises patient safety and the quality of care and increases the rate of misdiagnosis (3).

During the COVID-19 pandemic, physicians should closely monitor all possible scenarios in patients to minimize the possibility of medical errors. Misdiagnosis is defined as failing to precisely or promptly diagnose a clinical condition (4, 5). Herein, we report the case of an old woman presenting with fever, cough, and shortness of breath initially misdiagnosed as COVID-19, which resulted in a delayed diagnosis of lymphoma and the demise of the patient.

2. Case Presentation

We report a 73-year-old married female who was brought to our emergency department by her son during the early phase of the COVID-19 pandemic in Iran (March 24, 2020). The patient was fully conscious and complained of cough, shortness of breath, fatigue, myalgia, chills, and fever. She reported contact with her family members who tested positive for COVID-19 (i.e., her husband and her son). The medical history included diabetes mellitus, hypertension, asthma, and chronic renal disease. Her clinical examination was unremarkable except for splenomegaly.

On admission to the emergency department, fever (38°C), dyspnea (a respiratory rate of 28 breaths/min), and oxygen saturation of 90% in room air were recorded for the patient. Bilateral inspiratory crackles were also reported for the patient. Moreover, the chest X-ray and computed tomographic (CT) scan of the lung revealed bilateral interstitial markings and bilateral hilar lymphadenopathy with lower bilateral interstitial lung densities (Figure 1A). Laboratory investigations were prominent regarding elevated C-reactive protein (26.8 mg/dL, normal range: < 6) and lactate dehydrogenase (1705 U/L, normal range: 230 - 480), as well as thrombocytopenia (platelet count: 90 $\times$ 1000/μL, normal range: 140 - 450). No evidence of myeloproliferative neoplasms was observed in bone marrow aspiration.

Echocardiography showed an ejection fraction of 55% and mild left ventricle hypertrophy. Hepatosplenomegaly and lymphadenopathy in the porta hepatis and coeliac axis were detected in abdominal ultrasound. The results of nasopharyngeal swab testing for multiple respiratory pathogens, including SARS-CoV-2, were negative using multiplex polymerase chain reaction on admission. However, the initial diagnosis was COVID-19 infection. She stayed at home for two weeks and did not appear in any public place. Her condition improved with hydration, analgesics (acetaminophen), and antibiotics (azithromycin).

Four months later, the patient was readmitted to the hospital for upper gastrointestinal (GI) bleeding. Various symptoms and signs not detected during her initial admission, including cervical lymphadenopathy and weight loss of about 20 kg in the last month, were evident upon careful examination. Upper GI endoscopy revealed mild pangastritis and duodenal erosion. Table 1 shows basic clinical parameters after visiting a specialist.

Table 2 shows the results of blood tests on readmission. Lymph node biopsy revealed diffuse large B-cell lymphoma (CD45 and CD20, positive diffuse; CD5, positive a few; Ki67, positive about 50%; MNF116, CD56, and S100, negative). Unfortunately, the patient passed away a week after readmission. Figure 1B shows a section of the lung CT scan on rehospitalization.

3. Discussion

We reported the case of a patient with a delayed diagnosis of lymphoma and, therefore, delayed onset of treatment during the COVID-19 pandemic. Similarly, Yousefzai and Bhimaraj reported a failure to diagnose ST-segment elevation due to myocardial infarction during the COVID-19 pandemic (5). During the pandemic, most diagnostic orientations were focused on COVID-19, driving out of mind many diseases with overlapped symptoms. Besides, retrospectively identifying the cases of missed or delayed diagnosis by reviewing medical records is a complicated task unless patients keep receiving similar care services. Therefore, most misdiagnoses remain undetected.

Based on the literature, individuals with a delayed onset of cancer therapy, even for one month, bear a 6 - 13% higher risk of mortality (6). Patient delay and health care system delay refer to the two-step interval from the onset of patient symptoms to therapy initiation. In line with the results of the current study, Dang-Tan et al. reported that the cancer subtype was associated with patient delay in those with leukemia, while the healthcare system delay was more related to lymphoma (7).

Even prior to the global outbreak of COVID-19, some studies in developed countries had noted delayed diagnosis of lymphoma as a serious concern (8, 9). Multiple barriers to diagnosis have been detected, namely non-specific symptoms, the lack of a distinct referral pathway for lymphadenopathy, and insufficient tissue biopsies for diagnosis (i.e., fine needle aspirates for cytology examinations have a low diagnostic yield for lymphoma) (10). Several studies have emphasized that lymphoma can be misdiagnosed as tuberculosis (TB), and in TB endemic regions, up to 85% of lymphoma cases may be at first misdiagnosed as TB (11, 12).

Moreover, major clinical symptoms (e.g., lymphadenopathy or splenomegaly) can be easily missed in emergency departments during the COVID-19 pandemic. Excisional lymph node biopsies were reduced or canceled due to the high workload of COVID-19 wards. Antel et al., in their study, proposed establishing a rapid-access lymph node biopsy clinic to reduce diagnostic delay for lymphoma amid the COVID-19 era (13).

The COVID-19 pandemic was a universal unparalleled incident greatly affecting all healthcare systems, and it is required for specialists to be well-prepared beforehand to encounter diagnostic dilemmas during such exceptional

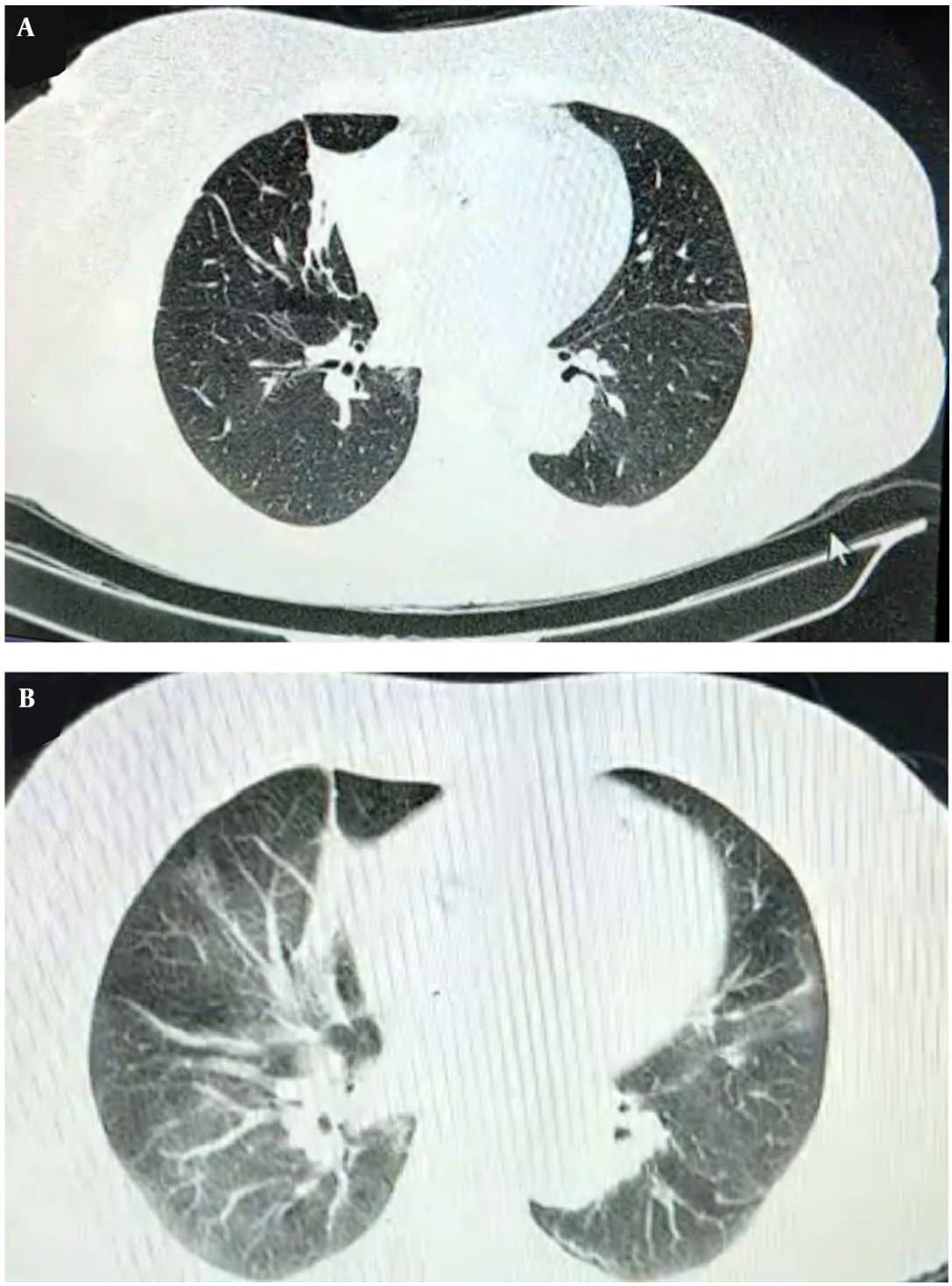

Figure 1. A section of the computed tomographic (CT) chest scan was performed in the first hospitalization (A); and four months later after rehospitalization (B)

Table 2. Hematologic Parameters on Rehospitalization

Test (Unit)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Reference Value
WBC $\times 10^3/mm^3$	13.9	9.3	7.9	5.4	3.7	4.4	4.1	4 - 11
RBC $\times 10^6/mm^3$	3.1	2.86	3.2	3.1	3.1	3.5	3.06	4.5 - 6.3
Hb (mg/dL)	8.6	7.8	9.5	9.2	8.9	10.3	8.7	14 - 18
HCT (%)	27.5	25.6	28	27.5	26.9	31.4	27.5	39 - 52
PLT $\times 10^3/\mu L$	35	25	24	27	25	28	25	140 - 450
Neutrophils (%)	78	45	64	53	58	60	65	4000 - 10000
Lymphocytes (%)	20	53	64	45	40	38	32	25 - 45
MCV (fL)	88.4	89.51	87.5	87.6	86.77	86.9	89.87	80.0 - 100
MCH (pg)	27.7	27.27	29.69	29.3	28.71	28.2	28.43	27 - 32
MCHC (g/dL)	31.3	30.47	33.93	33.5	33.1	32.5	31.64	31 - 36

Abbreviations: Hb, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PLT, platelet count; RBC, red blood cell count; WBC, white blood cell count.

conditions (14). The COVID-19 pandemic affected the everyday tasks of health centers and reduced their capacity to deliver elective services, accentuating the necessity of patient triage and paying attention to probably overlapped disease presentations. Regulations and recommendations were constantly changing as the pandemic gradually developed, requiring further preparedness and resilience among healthcare professionals to ensure patient safety and deliver satisfactory medical performance (15, 16).

3.1. Conclusions

In COVID-19 care units, it is necessary to consider the precise and periodic re-evaluation of individuals primarily diagnosed with COVID-19 to identify possibly missed diagnoses. The COVID-19 pandemic poses a new challenge to hematologists/oncologists who need to be more vigilant about lymphoma patients and enhance research efforts to optimize diagnostic algorithms for these patients during the COVID-19 pandemic.

Footnotes

Authors' Contribution: P. S. K.: Study design and coordination with authors; R. R.: Writing the manuscript, analysis, and interpretation of data, and assistance in the final revision of the manuscript; H. GH. and S. M. S. H. T.: Data analysis and participation in the final revision of the manuscript; A. R. and P. S. K.: Participation in the preparation and documentation of clinical evidence; A. R. B.: Study supervision.

Conflict of Interests: One of the authors (Alireza Bakhshipour) is the EIC of the journal. Based on the journal policy, this author was completely excluded from the review process of this article.

Ethical Approval: The local ethics committee affiliated with the Mazandaran University of Medical Sciences approved this study (ethical registration code: IR.MAZUMS.REC.1400.362). Protocols were in accordance with the principles of the Declaration of Helsinki.

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Table 1. Basic Clinical Parameters

Tests (Unit)	Result	Reference Value
Hematology		
WBC $\times 10^3/mm^3$	5.1	4000 - 10000
Neutrophils (%)	62	36 - 80
Lymphocytes (%)	36	16 - 51
RBC $\times 10^6/mm^3$	3.27	4.5 - 6.3
Hb (mg/dL)	10.4	14 - 18
HCT (%)	28.8	39 - 52
MCV (fL)	88.07	80.0 - 100
MCH (pg)	31.8	27 - 32
MCHC (g/dL)	36.11	31 - 36
ESR (mm/hr)	98	Up to 15
PT (Sec)	14.1	10 - 13
PT control (Sec)	11.5	70 - 100
INR (%)	1.3	0.9 - 1.0
PTT (Sec)	27	24 - 42
CRP	48	< 6
TIBC (μg/dL)	270	250 - 450
Biochemistry		
BUN (mg/dL)	63	7 - 23
Creatinine (mg/dL)	5.5	0.6 - 1.1
Serum Na (mEq/L)	135	135 - 145
Serum Ca (mg/dL)	6.2	8 - 10
Serum K (mEq/L)	3.5	3.5 - 5.2
Serum Mg (mg/dL)	2.3	1.5 - 2.5
AST (IU/L)	57	Up to 31
ALT (IU/L)	28	Up to 32
ALP (IU/L)	60	64 - 306
LDH (IU/L)	2100	225 - 500
Total bilirubin (mg/dL)	0.5	0.2 - 1.2
Direct bilirubin (mg/dL)	0.21	0 - 0.3
Amylase (U/L)	150	< 100
Fe (μg/dL)	152	35 - 155
CPK (IU/L)	40	Up to 170
ALB (g/dL)	3.9	3.5 - 5
ACE (ng/dL)	92	13.3 - 63.9
ANA (U)	0.62	Negative < 0.9; borderline 0.9 - 1.1; positive > 1.1
P-ANCA (U)	< 1/10	Negative < 1/10; positive > 1/10
C-ANCA (U)	< 1/10	Negative < 1/10; positive $\geq$ 1/10
Blood gas analysis (VBG)		

pH	7.34	7.31 - 7.41
PCO2 (mmHg)	42.2	35 - 40
HCO3(mEq/L)	22.5	22 - 26
PO2 (mmHg)	36.7	41 - 51
Urine analysis		
Color	Yellow	-
pH	5	4.5 - 8.0
Protein	Negative	Negative
Glucose	Negative	Negative
Blood	Positive (+++)	Negative
Urobilinogen	Normal	Negative
Bilirubin	Negative	Negative
Keton	Negative	Negative
Nitrite	Negative	Negative
WBC/h.p.f	10 - 12	0 - 5
RBC/h.p.f	Many	0 - 3
Epithelial cells/h.p.f	32 - 40	1 - 5
Bacteria	Moderate	0 - 1

Abbreviations: ACE, angiotensin-converting enzyme; ALB, albumin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ANA, antinuclear antibody; BUN, blood urea nitrogen; Ca, calcium; C-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; CPK, creatine phosphokinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Fe, ferrum (total iron); Hb, hemoglobin; HCT, hematocrit; INR, International normalized ratio; PLT, platelet cell; LDH, lactate dehydrogenase; K, potassium; Na, sodium; Mg, magnesium; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; P-ANCA, peripheral antineutrophil cytoplasmic antibodies; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell count; TIBC, total iron-binding capacity; WBC, white blood cell count.